

REMARKS

The Examiner is thanked for having graciously held a telephone interview with the undersigned on May 9, 2003.

The application and the Advisory Action of April 23, 2003 were discussed. It was agreed that claim 1 be amended to include recitations that " CO_2R^3 is CO_2H , a carboxylate salt or a carboxy protected by benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus- containing group, an oxime radical of formula $-\text{N}=\text{CHR}^7$ where R^7 is aryl or heterocyclic, or an *in vivo* hydrolysable ester group." It was also agreed that claim 23 be amended to include the definitions of various substituents of structure III, but not structure III itself. It was further agreed that claim 11 be amended to include a recitation to boronate groups listed on page 12, lines 20-27 of the original specification.

As stated in the April 23, 2003 Advisory Action, the amendments to claims 1, 11 and 21-23 made in the March 10, 2003 Response Under §1.116 were not entered for allegedly raising new issues. Therefore, the present Amendment does not take into account the amendments made in the March 10, 2003 Response.

Claims 1-18 and 21-24 were pending in the present application. Claims 1, 2, 11 and 21-23 are amended. Support for the amendments to claim 1 can be found, *inter alia*, on page 3, lines 5-8 and lines 12-19 as well as page 1, lines 13-14 of the original specification. Support for the amendment to claim 11 can be found, *inter alia*, on page 12, lines 20-27 of the original specification. The amendments to claims 2, 21 and 22 involve correcting informalities and do not raise any issue of new matter. Support for the amendments to claim 23 can be found, *inter alia*, on page 3, lines 5-8 and lines 12-19 as well as page 1, lines 13-14 of the original specification as well as in the original claim 1. Therefore, the present Amendment is fully supported by the original specification and does not raise any issue of new matter. In addition, the present Amendment would fully address all issues raised in the April 26, 2003 Advisory Action and thus, place the present application in condition for allowance. Accordingly, entry of the present

Amendment and withdrawal of various rejections are respectfully requested.

The Examiner is encouraged to contact the undersigned at (860) 686-1652 if he has any questions regarding the present Amendment.

Respectfully submitted,

Date: June 2, 2003

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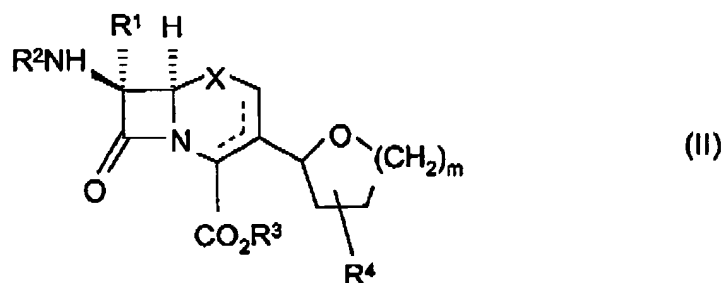
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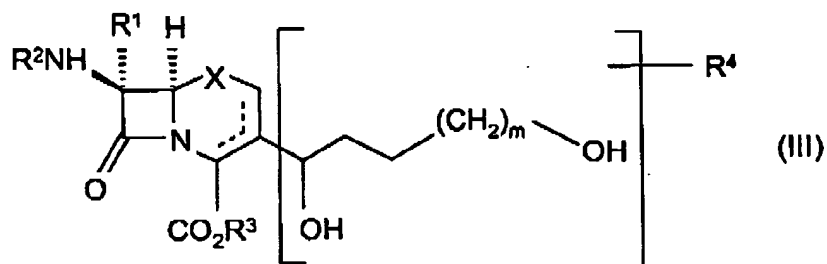
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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

1. (Twice Amended) A process for the preparation of a compound of formula (II):



comprising cyclizing a compound of formula (III):

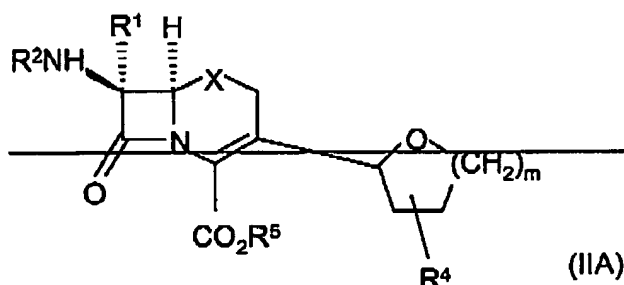
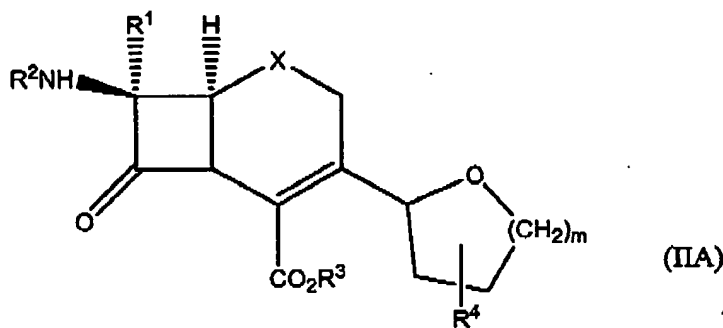


wherein in formulae (II) and (III), R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; CO_2R^3 is CO_2H , a carboxylate salt or a carboxy group protected by benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula $-N=CHR^7$ where R^7 is aryl or heterocyclic, or an *in vivo* hydrolysable ester group; R^3 is hydrogen or a carboxy-protecting group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R , $CONR_2$, SO_2NR_2 (where R is hydrogen or

C₁₋₆ alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO₂, O, or CH₂; and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s) R⁴ when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain,

and, when R³ is hydrogen optionally forming the carboxylate salt of said compound of formula III.

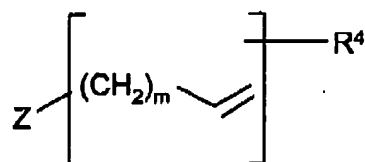
2. (Twice Amended) The process according to claim 1 wherein the compound of formula (II) is a 3-cephem of formula (IIA) or a pharmaceutically acceptable salt or pharmaceutically acceptable *in vivo* hydrolyzable ester thereof:



wherein R¹, R², R⁴, m and X are as defined with respect to formula (III) and the group CO₂R⁵ is CO₂R³ where CO₂R³ is a carboxyl group, a protected carboxyl group or a carboxylic acid salt.

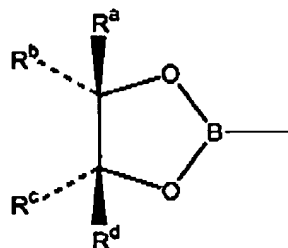
11. (Twice Amended) The process according to Claim 1 or 2, wherein the compound of formula III is prepared by coupling a compound of formula (IV) (as

defined in claim 10) with an organometallic reagent or a compound having the structure (IX)

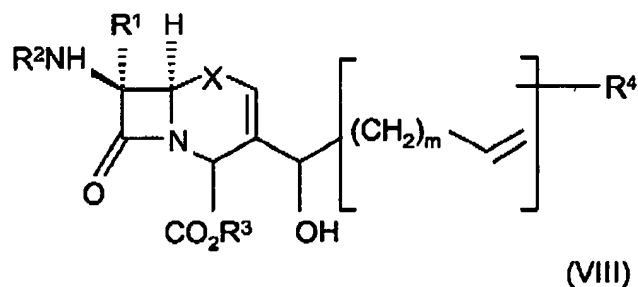


(IX)

wherein Z is boronate group (X)



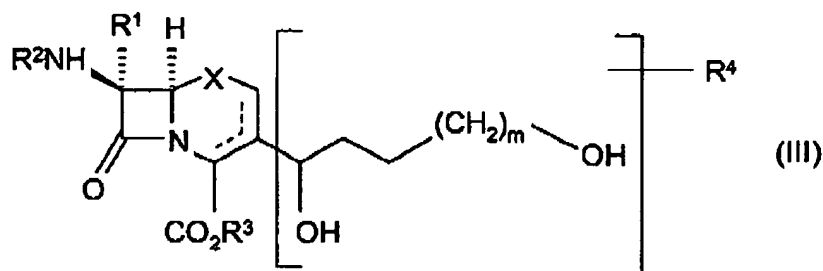
wherein R^a, R^b, R^c and R^d are independently selected from hydrogen, alkyl and protected carboxy to form a compound of formula (VIII):



(VIII)

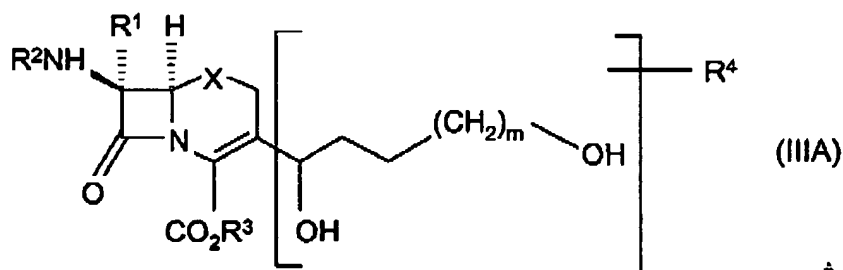
and wherein said compound of formula VIII is then hydroxylated to form a compound of formula III, where R¹, R², R³, R⁴, m, and X are as defined with respect to formula (III).

21. (Twice Amended) A compound of formula (III),

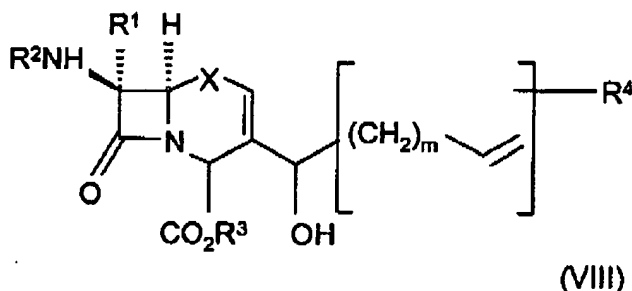


wherein R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; R^3 is hydrogen or a carboxy protecting group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R , $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO_2 , O, or CH_2 ; and m is 1 or 2; and the dotted line indicates that the compound may be a 2-cephem or a 3-cephem system, and where the substituent(s) R^4 when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.

22. (Amended) The compound according to Claim 21, wherein the compound is a compound of formula IIIA 3-cephem system, (IIIA).



23. (Amended) A compound of formula VIII, wherein R^1 , R^2 , R^3 , R^4 , and m are defined with respect to formula III.



wherein R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; CO_2R^3 is CO_2H , a carboxylate salt or a carboxy group protected by benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula $-N=CHR^7$ where R^7 is aryl or heterocyclic, or an *in vivo* hydrolysable ester group; R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R , $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO_2 , O, or CH_2 ; and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s) R^4 when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.